

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074647

Trade Name : FLURBIPROFEN TABLETS USP 50 AND 100MG

Generic Name: Flurbiprofen Tablets USP 50mg and 100mg

Sponsor : Sidmak Laboratories, Inc.

Approval Date: April 1, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074647

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074647

APPROVAL LETTER

APR 1 1997

Sidmak Laboratories, Inc.
Attention: Jairaj U. Mehta
17 West Street
P.O. Box 371
East Hanover, NJ 07936

APRIL 1 1997

Dear Sir:

This is in reference to your abbreviated new drug application dated March 14, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Flurbiprofen Tablets USP, 50 mg and 100 mg.

Reference is also made to your amendments dated March 11, and October 30, 1996, and February 25, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Flurbiprofen Tablets USP, 50 mg and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Ansaid® Tablets 50 mg and 100 mg, respectively, of Pharmacia and Upjohn Co. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

4/1/97
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074647

FINAL PRINTED LABELING

Central Nervous System: Ataxia, cerebrovascular ischemia, confusion, paresthesia, and twitching.
Hematologic: Decrease in hemoglobin and hematocrit; iron deficiency anemia, hemolytic anemia and aplastic anemia; leukopenia; eosinophilia; ecchymosis and thrombocytopenia. (See also **PRECAUTIONS: Effect On Platelets and Coagulation.**)
Respiratory: Asthma and epistaxis.
Dermatologic: Angioedema, urticaria, eczema, and pruritus; photosensitivity, toxic epidermal necrolysis, and exfoliative dermatitis.
Special Senses: Conjunctivitis and parosmia.
Genitourinary: Hematuria and renal failure; interstitial nephritis.
Body as a Whole: Chills and fever; anaphylactic reaction.
Metabolic/Nutritional: Hyponatremia.

Cardiovascular: Heart failure, hypertension, vascular diseases and vasodilation.
Incidence Less Than 1% (Causal Relationship Unknown): The following reactions have been reported in patients taking flurbiprofen under circumstances that do not permit a clear attribution of the reaction to flurbiprofen. These reactions are being included as alerting information for physicians. Adverse reactions reported only in worldwide postmarketing experience or the literature (which presumably indicates that they are rarer) are italicized.
Gastrointestinal: Peridontal abscess, appetite changes, cholecystitis, and dry mouth.
Central Nervous System: Convulsion, meningitis, hypertonia, cerebrovascular accident, emotional lability, and subarachnoid hemorrhage.
Hematologic: Lymphadenopathy.
Respiratory: Bronchitis, laryngitis, dyspnea, pulmonary embolism, pulmonary infarct, and hyper-ventilation.

Dermatologic: Alopecia, nail disorder, herpes simplex, zoster, dry skin, and sweating.
Special Senses: Ear disease, corneal opacity, glaucoma, retrobulbar neuritis, changes in taste, and transient hearing loss; retinal hemorrhage.
Genitourinary: Menstrual disturbances, vaginal and uterine hemorrhage, vulvovaginitis, and prostatic disease.

Metabolic/Nutritional: Hyperkalemia.
Cardiovascular: Arrhythmias, angina pectoris, and myocardial infarction.
Musculoskeletal: Myasthenia.

DRUG ABUSE AND DEPENDENCE: No drug abuse or drug dependence has been observed with flurbiprofen.

OVERDOSSAGE: Information on overdosage is available for 13 children and 12 adults. Nine of the 13 children were less than 6 years old. Drowsiness occurred after doses of 150 to 800 mg in 3 of these young children (with dilated pupils in 1), and in a 2-year-old who also had semi-consciousness, pinpoint pupils, diminished tone, and elevated liver enzymes. Other children who ingested doses of 200 mg to 2.5 g showed no symptoms.

Among the adults, a 70-year-old man with a history of chronic obstructive airway disease died. Toxicological analysis showed acute flurbiprofen overdose and a blood ethanol concentration of 100 mg/dL. In the other cases, symptoms were as follows: coma and respiratory depression after 3 to 6 g; drowsiness, nausea and epigastric pain after 2.5 to 5 g; epigastric pain and dizziness after 3 g; headache and nausea after ≤2 g; agitation after 1.5 g; and drowsiness after 1.0 g. One patient, who took 200 to 400 mg flurbiprofen and 2.4 g fenpropfen, had disorientation and diplopia. Three adults had no symptoms after 3 to 5 g flurbiprofen.

Treatment of an overdose: the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Supportive treatment should be instituted as necessary. Some patients have been given supplemental oral or intravenous fluids and required no other treatment.

In mice, the flurbiprofen LD₅₀ was 750 mg/kg when administered orally and 200 mg/kg when administered intraperitoneally. The primary signs of toxicity were prostration, ataxia, loss of righting reflex, labored respiration, twitches, convulsions, CNS depression, and splayed hind limbs. In rats, the flurbiprofen LD₅₀ was 160 mg/kg when administered orally and 400 mg/kg when administered intraperitoneally. The primary signs of toxicity were tremors, convulsions, labored respiration, and prostration. These were observed mostly in the intraperitoneal studies.

DOSAGE AND ADMINISTRATION: Flurbiprofen tablets are administered orally.
 Rheumatoid arthritis and osteoarthritis: Recommended starting dose is 200 to 300 mg total daily dose administered BID, TID, or QID. (Most experience in rheumatoid arthritis has been with TID or QID dosage.) The largest recommended single dose in a multiple-dose daily regimen is 100 mg. The dose should be tailored to each patient according to the severity of the symptoms and the response to therapy.

Although a few patients have received higher doses, doses above 300 mg per day are not recommended until more clinical experience with flurbiprofen is obtained.

HOW SUPPLIED: Flurbiprofen Tablets, USP

50 mg - Oblong, white film coated tablets printed with SL over 605 in black ink on one side. Available in bottles of 100's and 500's.
100 mg - Oblong, green film coated tablets printed with SL over 606 in black ink on one side. Available in bottles of 100's and 500's.

Dispense in a tight, light-resistant container as defined in the USP.

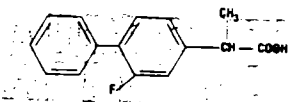
Store at controlled room temperature 15° to 30°C (59° to 86°F).

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
SIDMAK LABORATORIES, INC.
 East Hanover, NJ 07936

P08-0605

DESCRIPTION: Flurbiprofen is a nonsteroidal anti-inflammatory agent. Flurbiprofen is a phenylalkanoic acid derivative designated chemically as (±) 2-(2-Fluoro-4-biphenyl)propionic acid. The molecular formula is C₁₅H₁₃F₂O₂, with a molecular weight of 244.27. Flurbiprofen is a white or slightly yellow crystalline powder. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents. Its structural formula is:



APR 1 1996



P08-0605
**FLURBIPROFEN
 TABLETS, USP**

ISS. 11/95

Each tablet, for oral administration, contains 50 mg or 100 mg of flurbiprofen. In addition, each tablet contains the following inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, crospovidone, hydroxypropyl methylcellulose, anhydrous lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, propylene glycol, synthetic black iron oxide and titanium dioxide. The 100 mg tablet also contains FD&C Blue No. 1 Aluminum Lake and D&C Yellow No. 10 Aluminum Lake.

CLINICAL PHARMACOLOGY: Flurbiprofen is a nonsteroidal anti-inflammatory agent which has shown anti-inflammatory, analgesic, and antipyretic properties in pharmacologic studies. As with other such drugs, its mode of action is not known. However, it is a potent prostaglandin synthesis inhibitor, and this property may be involved in its anti-inflammatory effect.

Flurbiprofen is well absorbed after oral administration, reaching peak blood levels in approximately 1.5 hours (range 0.5 to 4 hours). Administration with food alters the rate of absorption but does not affect the extent of drug availability. The elimination half-life is approximately 6 hours with 90% of the half-life values from 3 to 9 hours. Individual half-life values ranged from 2.8 to 12 hours. There is no evidence of drug accumulation and flurbiprofen does not induce enzymes that alter its metabolism. Excretion of flurbiprofen is 88% to 98% complete 24 hours after the last dose.

Flurbiprofen is extensively metabolized and excreted primarily in the urine, about 20% as free and conjugated drug and about 50% as hydroxylated metabolites. About 90% of the flurbiprofen in urine is present as conjugates. The major metabolite, 4'-hydroxy-flurbiprofen, has been detected in human plasma, but in animal models of inflammation this metabolite showed little anti-inflammatory activity. Flurbiprofen is more than 99% bound to human serum proteins.

In a reported study the average maximum serum concentration of flurbiprofen, following a 100 mg oral dose of flurbiprofen tablets in normal volunteers (n=184), was 15.2 mcg/ml, with 90% of the values between 10 and 22 mcg/ml. In geriatric subjects (n=7) between the ages of 58 and 77 years, 100 mg flurbiprofen resulted in an average peak drug level of 18.0 mcg/ml and an average elimination half-life of 6.5 hours (range 3 to 10 hours). In geriatric rheumatoid arthritis patients (n=13) between the ages of 65 and 83 years receiving 100 mg flurbiprofen, the average maximum blood level was 12.7 mcg/ml and the average elimination half-life was 5.6 hours (range 4 to 10 hours).

In a study assessing flurbiprofen pharmacokinetics in end stage renal disease (ESRD), mean urinary recovery of a 100 mg dose was 73% in 48 hours for 9 normal subjects and 17% in 96 hours for 8 ESRD patients under-going continuous ambulatory peritoneal dialysis. Plasma concentrations of flurbiprofen were about 40% lower in the ESRD patients; the elimination half-life of flurbiprofen was unchanged. Elimination of the 4'-hydroxy-flurbiprofen metabolite was markedly reduced in the ESRD patients. The pharmacokinetics of flurbiprofen in patients with decreased renal function but not ESRD have not been determined.

The pharmacokinetics of flurbiprofen in patients with hepatic disease have not been determined.

The efficacy of flurbiprofen tablets has been demonstrated in patients with rheumatoid arthritis and osteoarthritis. Using standard assessments of therapeutic response, flurbiprofen (200 to 300 mg/day) demonstrated effectiveness comparable to aspirin (2000 to 4000 mg/day), ibuprofen (2400 to 3200 mg/day), and indomethacin (75 to 150 mg/day).

In patients with rheumatoid arthritis, flurbiprofen may be used in combination with gold salts or corticosteroids.

INDICATIONS AND USAGE: Flurbiprofen tablets are indicated for the acute or long-term treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

CONTRAINDICATIONS: Flurbiprofen tablets are contraindicated in patients who have previously demonstrated hypersensitivity to the product. Flurbiprofen should not be given to patients in whom flurbiprofen, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions. Fatal asthmatic reactions have been reported in such patients receiving this type of drug.

WARNINGS: Risk of Gastrointestinal (GI) Ulcerations, Bleeding and Perforation with Nonsteroidal Anti-inflammatory Therapy:

Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with nonsteroidal anti-inflammatory drugs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials of such agents for several months to two years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

ISS. 11/95

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory agents in causing such reactions. High doses of any such agent probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to off-set the potential increased risk of GI toxicity.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

PRECAUTIONS: General Precautions: Impaired Renal or Hepatic Function: As with other nonsteroidal anti-inflammatory drugs, flurbiprofen should be used with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Studies to assess the pharmacokinetics of flurbiprofen in patients with decreased liver function have not been done.

Renal Effects: Toxicology studies in rats have shown renal papillary necrosis at dosage levels equivalent to a mg/kg basis to those used clinically in humans. Similar findings were seen in monkeys given high doses (50 to 100 mg/kg, or approximately 20 to 40 times the human therapeutic dose) for 90 days.

In clinical studies, kidney function tests were done at least monthly in patients taking flurbiprofen. In these studies, renal effects of flurbiprofen were similar to those seen with other nonsteroidal anti-inflammatory drugs.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Those patients at high risk who chronically take flurbiprofen should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

The elimination half-life of flurbiprofen was unchanged in patients with end stage renal disease (ESRD). Flurbiprofen metabolites are primarily eliminated by the kidneys and elimination of 4-hydroxy-flurbiprofen was markedly reduced in ESRD patients. Therefore, patients with significantly impaired renal function may require a reduction of dosage to avoid accumulation of flurbiprofen metabolites and should be monitored. (See also the CLINICAL PHARMACOLOGY section.)

Liver Tests: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with flurbiprofen.

Anemia: Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients who have initial hemoglobin values of 10 g/dL or less, and who are to receive long-term therapy, should have hemoglobin values determined periodically.

Fluid Retention and Edema: Fluid retention and edema have been reported; therefore, flurbiprofen should be used with caution in patients with cardiac decompensation, hypertension, or similar conditions.

Vision Changes: Blurred and/or diminished vision has been reported with the use of flurbiprofen and other nonsteroidal anti-inflammatory drugs. Patients experiencing eye complaints should have ophthalmologic examinations.

Effect on Platelets and Coagulation: Flurbiprofen inhibits collagen-induced platelet aggregation. Prolongation of bleeding time by flurbiprofen has been demonstrated in humans after single and multiple oral doses. Patients who may be adversely affected by prolonged bleeding time should be carefully observed when flurbiprofen is administered.

Information for Patients: Flurbiprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits of nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and the physician.

Drug Interactions: Antacids: Administration of flurbiprofen tablets to volunteers under fasting conditions, or with antacid suspension, yielded similar serum flurbiprofen-time profiles in young subjects (n=12). In geriatric subjects (n=7) there was a reduction in the rate but not the extent of flurbiprofen absorption.

Anticoagulants: Flurbiprofen, like other nonsteroidal anti-inflammatory drugs, has been shown to affect bleeding parameters in patients receiving anticoagulants, and serious clinical bleeding has been reported. The physician should be cautious when administering flurbiprofen to patients taking anticoagulants.

Aspirin: Concurrent administration of aspirin and flurbiprofen resulted in 50% lower serum flurbiprofen concentrations. This effect of aspirin (which also lowers serum concentrations of other

nonsteroidal anti-inflammatory drugs given with it) has been demonstrated in patients with rheumatoid arthritis (n=15) as well as normal volunteers (n=16). Concurrent use of flurbiprofen and aspirin is therefore not recommended.

Beta-adrenergic Blocking Agents: The effect of flurbiprofen on blood pressure response to propranolol and atenolol, was evaluated in men with mild uncomplicated hypertension (n=10). Flurbiprofen pretreatment attenuated the hypotensive effect of a single dose of propranolol but not atenolol. Flurbiprofen did not appear to affect the beta-blocker-mediated reduction in heart rate. Flurbiprofen did not affect the pharmacokinetic profile of either drug, and the mechanism underlying the interference with propranolol's hypotensive effect is unknown. Patients taking both flurbiprofen and a beta-blocker should be monitored to ensure that a satisfactory hypotensive effect is achieved.

Cimetidine, Ranitidine: In normal volunteers (n=9), pretreatment with cimetidine or ranitidine did not affect flurbiprofen pharmacokinetics, except that a small (13%) but statistically significant increase in the area under the serum concentration curve of flurbiprofen resulted with cimetidine.

Digoxin: Studies of concomitant administration of flurbiprofen and digoxin to healthy men (n=14) did not show a change in the steady-state serum levels of either drug.

Diuretics: Studies in normal volunteers have shown that flurbiprofen, like other nonsteroidal anti-inflammatory drugs, can interfere with the effects of furosemide. Although results have varied from study to study, effects have been shown on furosemide-stimulated diuresis, natriuresis, and kaliuresis. Other nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis have been shown to interfere with thiazide diuretics in some studies, and with potassium-sparing diuretics. Patients receiving flurbiprofen and furosemide or other diuretics should be observed closely to determine if the desired effect is obtained.

Oral Hypoglycemic Agents: In one study, flurbiprofen was given to adult diabetics who were already receiving glyburide (n=4), metformin (n=2), chlorpropamide with phenformin (n=3), or glyburide with phenformin (n=6). Although there was a slight reduction in blood sugar concentrations during concomitant administration of flurbiprofen and hypoglycemic agents, there were no signs or symptoms of hypoglycemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility: An 80-week study in mice at doses of 2, 5, and 12 mg/kg/day and a 2-year study in rats at doses of 0.5, 2, and 4 mg/kg/day did not show evidence of carcinogenicity at maximum tolerated doses of flurbiprofen.

Flurbiprofen did not impair the fertility of male or female rats treated orally at 2.25 mg/kg/day for 65 days and 16 days, respectively, before mating.

Teratogenic Effects: Pregnancy Category B. In teratology studies flurbiprofen, given to mice in doses up to 12 mg/kg/day, to rats in doses up to 25 mg/kg/day, and to rabbits in doses up to 7.5 mg/kg/day, showed no teratogenic effects.

Because there are no adequate and well-controlled studies in pregnant women, and animal teratology studies do not always predict human response, flurbiprofen is not recommended for use in pregnancy.

Labor and Delivery: Flurbiprofen's effects on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use of flurbiprofen during late pregnancy is not recommended.

Nursing Mothers: Concentrations of flurbiprofen in breast milk and plasma of nursing mothers suggested that a nursing infant could receive approximately 0.10 mg flurbiprofen per day in the established milk of a woman taking 200 mg/day. Because of possible adverse effects of prostaglandin-inhibiting drugs on neonates, flurbiprofen is not recommended for use in nursing mothers.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reaction information was derived from patients who received flurbiprofen in blinded-controlled and open-label clinical trials, and from worldwide marketing experience and from publications. In the description below, rates of the more common events (greater than 1%) and many of the less common events (less than 1%) represent clinical study results. For rarer events that were derived principally from worldwide marketing experience and the literature (printed in *italics*), accurate rate estimates are generally impossible.

Of the 4123 patients in premarketing studies, 2954 were treated for at least 1 month, 1448 for at least 3 months, 948 for at least 6 months, 356 for at least 1 year, and 100 for at least 2 years. Of the 4123 patients, 9.4% dropped out of the studies because of an adverse drug reaction, principally involving the gastrointestinal tract (5.8%), central nervous system and special senses (1.4%), skin (0.6%), and genitourinary tract (0.5%).

Incidence Greater Than 1%: An asterisk after a reaction identifies reactions which occurred in 3 to 9% of patients treated with flurbiprofen. Reactions occurring in 1 to 3% of the patients are unmarked.

Gastrointestinal: Dyspepsia*, diarrhea*, abdominal pain*, nausea*, constipation, GI bleeding, flatulence, elevated liver enzymes, and vomiting.

Central Nervous System: Headache*, nervousness, and other manifestations of CNS "stimulation" (e.g., anxiety, insomnia, reflexes increased, and tremor), and symptoms associated with CNS "inhibition" (e.g., amnesia, asthenia, somnolence, malaise, and depression).

Respiratory: Rhinitis.

Dermatological: Rash.

Special Senses: Dizziness, tinnitus, and changes in vision.

Genitourinary: Signs and symptoms suggesting urinary tract infection*.

Body as a Whole: Edema*.

Metabolic/Nutritional: Body weight changes.

Incidence Less Than 1% (Causal Relationship Probable): The reactions listed in this category occurred in <1% of patients in the clinical trials or were reported during postmarketing experience from other countries. Adverse reactions reported only in worldwide postmarketing experience or the literature (which presumably indicates that they are rarer) are *italicized*.

Gastrointestinal: Peptic ulcer disease (see also WARNINGS: Risk of Gastrointestinal (GI) Ulcerations, Bleeding and Perforation with Nonsteroidal Anti-inflammatory Therapy), gastritis, bloody diarrhea, stomatitis, esophageal disease, hematemesis, and hepatitis; *cholestatic and non-cholestatic jaundice*.

NDC 50111-605-01

**Flurbiprofen
Tablets, USP**

50 mg

CAUTION: Federal law prohibits
dispensing without prescription.
100 Tablets

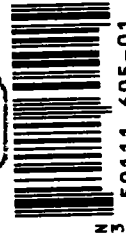
Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Flurbiprofen, USP..... 50 mg
Dispense in a tight, light-resistant container as
defined in the USP.
Store at controlled room temperature 15°-30°C

USUAL DOSAGE: See package insert.
Control No.
Exp. Date
Lot No.

APR 1 1997

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936



50111-605-01

NDC 50111-605-02

**Flurbiprofen
Tablets, USP**

50 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:
Flurbiprofen, USP..... 50 mg
Dispense in a tight, light-resistant
container as defined in the USP.
Store at controlled room temperature
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Control No.
Exp. Date
Lot No.

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APR 1 1997



50111-605-02

NDC 50111-606-02

Flurbiprofen Tablets, USP

100 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:

Flurbiprofen, USP 100 mg

Dispense in a tight, light-resistant
container as defined in the USP

Store at controlled room temperature
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert



50111-606-02

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Control No.:
Exp. Date:
Rev. 10/95

APR 1 1997

NDC 50111-606-01

Flurbiprofen Tablets, USP

100 mg

CAUTION: Federal law prohibits
dispensing without prescription.

100 Tablets

Sidmak.
LABORATORIES, INC.

EACH TABLET CONTAINS:

Flurbiprofen, USP 100 mg

Dispense in a tight, light-resistant container as
defined in the USP.

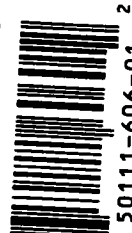
Store at controlled room temperature 15°-30°C
(59°-86°F).

USUAL DOSAGE: See package insert.

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APR
APR



50111-606-01

APR 1 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074647

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4
2. ANDA # 74-647
3. NAME AND ADDRESS OF APPLICANT
Sidmak
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936
4. LEGAL BASIS FOR ANDA SUBMISSION:
Patent expiration and no exclusivity.
5. SUPPLEMENT(S): N/A
6. PROPRIETARY NAME : N/A
7. NONPROPRIETARY NAME
Flurbiprofen
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
March 14, 1995: Date of submission
February 25, 1997: Amendment
10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
NSAID Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM 14. POTENCY
Tablets 50 mg, 100 mg
16. RECORDS AND REPORTS: N/A
18. CONCLUSIONS AND RECOMMENDATIONS: Approvable

See comments Section

19. REVIEWER: DATE COMPLETED:
Dave Gill March 12 , 1997
- cc: ANDA 74-647
Division File
DUP File
Field Copy

Endorsements:

HFD-623/D.Gill/3/12/97

HFD-623/V.Sayeed/3/13/97

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F/T by: gp/3/20/97

3/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074647

BIOEQUIVALENCE REVIEW(S)

ANDA 74-647

Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. BOX 371
East Hanover NJ 07936
|||||

DEC - 2 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Flurbiprofen Tablets USP, 50 mg and 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Flurbiprofen Tablets, USP
50 mg & 100 mg
ANDA # 74-647
Reviewer: S.P. Shrivastava
WP # 74647SDW.D95

NOV 26 1996

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
~~December 8, 1995~~
3/11/96; 10/30/96

**REVIEW OF LIMITED FOOD STUDY, DISSOLUTION DATA
AND WAIVER REQUEST**

I. BACKGROUND

Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis and osteoarthritis. Flurbiprofen inhibits prostaglandin synthesis, which may be associated with its mechanism of action. Virtually all of the anti-inflammatory activity of flurbiprofen is present in the S-(+)-enantiomer. The available evidence from human studies indicates that R-flurbiprofen does not undergo the *in vivo* irreversible inversion to the S-enantiomer that has been observed in other NSAID's of the 2-arylpropionic acid class.

Flurbiprofen is rapidly absorbed following oral administration with T_{max} ranging 0.5 to 4 hrs. Food may decrease C_{max} (27-32%) by delaying absorption but does not significantly change the extent of absorption as measured by AUC. In one study, flurbiprofen absorption was found to be bimodal after administration of the tablet form in the fasted (on water) or fed (on apple juice) state. In this study, the lag time before the onset of the second absorption phase was dependent on the gastric emptying time.

Flurbiprofen is greater than 99% bound to plasma proteins (albumin). The binding has been reported to be minimally nonlinear over the concentration ranges encountered clinically. In one study, however, AUC_{0-inf} was found increased linearly over the dose range of 100-300 mg. Flurbiprofen elimination from plasma appears biphasic, with terminal half-life values reported from 3 to 7 hours. The major route of elimination is hepatic clearance, with 95% of a daily dose excreted in urine in 24 hours, either as unchanged drug (20-25%), or as three metabolites: 4'-hydroxy (40-47%), 3'-hydroxy-4'-methoxy (20-30%), and 3',4'-dihydroxy (5%). The 4'-hydroxy metabolite showed low pharmacological activity in animal models.

Common adverse reactions from flurbiprofen include dyspepsia, diarrhea, abdominal pain, nausea, headache, signs and symptoms suggesting urinary tract infection and edema.

Flurbiprofen is currently marketed as Ansaïd^R, 50 and 100 mg tablets, manufactured by Upjohn.

The firm has previously submitted an acceptable single-dose fasting study on 100 mg tablets, and comparative dissolution data for 100 and 50 mg tablets (Re: review by Shrivastava, 8/31/95). In this submission, the firm has responded to the deficiency by providing data on non-fasting study and additional dissolution testing.

II. NON-FASTING STUDY: PROTOCOL #930162

1. Study Objective and Design

The purpose of this study was to evaluate the bioequivalency of Sidmak Laboratories' Flurbiprofen Tablets, 100 mg, and Upjohn's Ansaid^R Tablets, 100 mg, under fed conditions and to examine the effect of food on the test product. The study design included three-treatments, six-sequences, and three-periods.

The study was conducted at _____ . The principal investigator:
Co-Investigator: _____ Plasma samples were also
assayed by _____ Study dates were: November 28, 1995-December 13, 1995.
Analysis dates: December 15, 1995-January 12, 1996.

Eighteen normal, healthy adult male volunteers entered , and 17 completed the study. Subject #12 was withdrawn due to drug adverse reaction. Subject #17 was given acetaminophen (2x500 mg) during Period 3, 10.5 hours post-dosing.

The subjects were between 18-45 years of age, and weighing at least 60 kg and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three treatment, three period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. Subjects especially did not have any history of: allergy to flurbiprofen, aspirin, on any other nonsteroidal anti-inflammatory drug; history or presence of pulmonary, gastrointestinal, hepatic, renal, cardiovascular, endocrine, immunologic, dermatologic, neurologic or psychiatric or hematological diseases; asthma, rhinitis or urticaria; ulcers, nasal polyps, hypertension, abnormal bleeding or angioedema; alcohol or drug abuse within the last year; donated blood; or have completed another study in the last 28 days. They were free of all medications at least 7 days prior to each study period and allowed no concomitant medications during the study period. No alcohol was allowed for 24 hours before and through the sample collection period. No caffeine or xanthine containing products were allowed for 24 hours prior to and during the time samples were collected. The subjects fasted overnight pre-dosing and 4 hours post-dosing. The washout duration between phases was one week.

Test Regimen: A: Single oral 100 mg dose administered with 240 mL of water at ambient temperature.

B and C: Single oral 100 mg dose administered with 240 mL of water at ambient temperature. 30 minutes after administration of a standard breakfast.

The three treatments consisted of a single 100 mg dose of either the test product. Sidmak Laboratories' flurbiprofen tablets, 100 mg, Lot # 93-022T (Batch size of _____ units, potency _____)

of 96.5%; RSD=0.48%), or the reference product. Upjohn's Ansaïd^R tablets. 100 mg, Lot # 198JC (Exp. date: 4/99, potency 98.4%; RSD=0.83%), taken orally with 240 mL of water. In the previous fasting and dissolution studies, the firm used the same test lot, but a different reference lot, Lot # 482YP (Exp. date: 2/98; potency 99.9%; RSD=1.2%). The reason for changing the reference lot was insufficient supply at hand for the full non-fasting study.

Blood samples (1 x 5 mL) were collected in Vacutainers containing EDTA at 0 (pre-dose) and at 0.167, 0.33, 0.5, 0.67, 0.83, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dosing.

2. Assay Methodology

3. Results

A. Plasma Concentration Time Profile

Mean flurbiprofen levels in plasma, and ratios between treatments, with and without Subject #12, are given in the Tables 1-2 and 7-8, respectively. Ratios for test/reference (fed) varied between 0.84-1.63 during 1-24 hours post-dose period. The graphical profiles are shown in Attachment-1.

B. Pharmacokinetic Parameters

- The pharmacokinetic parameters, ratios of PK parameters for treatments, and statistical results are given in Tables 3-6, 9-12 and Attachments 2-4.
- ANOVA analysis did not show any significant period or sequence effect on AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , or T_{max} .

- The test/reference ratios for average PK parameters for the products were within 0.8-1.2 as required (Tables 4, 10). Exclusion/Inclusion of Subjects #12 and/Subject #17, does not change the results (Tables 4, 10, Attachments 2-4).
- Ratios of individual $AUC_{0-t}/AUC_{0-\infty}$ averaged 0.92 (range: 0.88-0.96).
- Individual PK parameters are given in Attachments 5-7.
- Food appears to decrease the and C_{max} and increase T_{max} values for the product (Tables 4, 10).

C. **Adverse Reaction:** No difference between test-fed and reference-fed were found.

Sign/Symptom	Test-Fed	Reference-Fed	Test-Fasting	Drug Related
Headache	0	1	1	Probable/Possible
Heartburn	2	1	1	Probable/Possible
Nausea	1	1	0	Probable/Possible
Stomach Ache	2	1	0	Probable/Possible

The *in vivo* non-fasting study is acceptable.

TABLE 1. MEAN PLASMA FLURBIPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (n=18)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.17	184.38	520.49	0.00	0.00	0.00	0.00
0.33	3551.70	3883.47	392.53	1405.30	272.54	793.74
0.5	7118.21	5460.87	1915.47	4529.84	884.02	1471.99
0.67	8576.48	5940.61	2838.50	5635.80	1734.53	2615.37
0.83	9532.92	5463.99	3569.32	4730.45	2334.18	3135.49
1	10653.88	4649.38	4574.12	4459.35	3091.28	3228.60
1.5	12212.69	3639.57	7016.37	4077.55	5341.04	3616.58
2	12075.26	2002.04	8409.03	2637.15	7501.72	3953.55
2.5	10716.21	1762.77	9074.58	1656.73	8729.51	4245.22
3	9276.95	2006.67	9048.07	1537.53	8485.48	2758.52
3.5	8161.13	1973.45	8873.19	2197.41	8351.23	2087.17
4	7298.74	1737.06	8280.97	2213.99	8632.14	2145.31
5	5533.17	1423.86	6358.07	1637.02	7542.82	2302.51
6	4199.88	1119.12	4957.77	1369.30	5526.44	1562.13
8	2754.78	971.69	3143.66	974.85	3474.07	1088.29
10	1910.95	802.63	2233.19	795.50	2440.87	880.98
12	1381.22	592.26	1618.74	677.30	1752.44	700.33
16	712.18	599.48	942.42	466.99	986.82	551.52
24	152.89	357.97	160.24	316.47	178.75	362.14
36	0.00	0.00	0.00	0.00	0.00	0.00

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 2. MEAN PLASMA FLURBIPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (n=18)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.17	.	.	.
0.33	9.05	13.03	1.44
0.5	3.72	8.05	2.17
0.67	3.02	4.94	1.64
0.83	2.67	4.08	1.53
1	2.33	3.45	1.48
1.5	1.74	2.29	1.31
2	1.44	1.61	1.12
2.5	1.18	1.23	1.04
3	1.03	1.09	1.07
3.5	0.92	0.98	1.06
4	0.88	0.85	0.96
5	0.87	0.73	0.84
6	0.85	0.76	0.90
8	0.88	0.79	0.90
10	0.86	0.78	0.91
12	0.85	0.79	0.92
16	0.76	0.72	0.96
24	0.95	0.86	0.90
36	.	.	.

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 3. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) (n=18)
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	73122.47	18285.26	68853.39	14878.78	70242.44	15284.08
AUCT	68056.71	16030.57	63669.67	13515.34	64479.06	13499.98
CMAX	15345.82	1933.76	11832.04	2786.95	11599.17	2559.99
KE	0.18	0.05	0.17	0.05	0.17	0.05
LAUCI	71233.23	0.23	67509.92	0.20	68818.18	0.20
LAUCT	66485.34	0.22	62488.57	0.19	63286.34	0.19
LCMAX	15239.87	0.12	11551.35	0.22	11350.17	0.21
THALF	4.15	1.36	4.45	1.18	4.40	1.25
TMAX	1.47	0.64	2.55	1.07	3.02	1.10

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 4. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) (n=18)
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.06	1.04	0.98
AUCT	1.07	1.06	0.99
CMAX	1.30	1.32	1.02
KE	1.09	1.07	0.98
LAUCI	1.06	1.04	0.98
LAUCT	1.06	1.05	0.99
LCMAX	1.32	1.34	1.02
THALF	0.93	0.94	1.01
TMAX	0.58	0.49	0.84

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 5. LSMEANS AND 90% CONFIDENCE INTERVALS (n=18)
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	73920.59	68853.39	70242.44	104.51	110.20	102.45
AUCT	68847.67	63669.67	64479.06	105.36	110.90	104.04
CMAX	15245.08	11832.04	11599.17	118.85	138.84	121.23
LAUCI	72082.37	67509.92	68818.18	104.07	109.55	102.09
LAUCT	67318.81	62488.57	63286.34	104.98	110.55	103.66
LCMAX	15096.44	11551.35	11350.17	119.29	143.18	121.40

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS (n=18)
UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	108.03	95.23	100.81
AUCT	109.51	96.01	101.48
CMAX	141.63	91.81	112.21
LAUCI	107.47	95.61	100.65
LAUCT	109.16	96.22	101.32
LCMAX	145.72	92.89	111.50

TABLE 7. MEAN PLASMA FLURBIPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (N=17)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.17	184.38	520.49	0.00	0.00	0.00	0.00
0.33	3551.70	3883.47	415.62	1445.03	139.36	574.62
0.5	7118.21	5460.87	2028.14	4643.18	688.07	1252.13
0.67	8576.48	5940.61	3005.47	5763.18	1493.89	2481.97
0.83	9532.92	5463.99	3710.06	4837.04	2105.07	3072.76
1	10653.88	4649.38	4710.35	4557.82	2895.79	3216.29
1.5	12212.69	3639.57	7092.58	4189.81	5251.89	3707.45
2	12075.26	2002.04	8445.14	2713.72	7408.80	4054.91
2.5	10716.21	1762.77	9053.71	1705.28	8679.05	4370.30
3	9276.95	2006.67	9061.53	1583.76	8412.44	2825.42
3.5	8161.13	1973.45	8885.31	2264.42	8344.00	2151.18
4	7298.74	1737.06	8300.32	2280.56	8676.34	2202.87
5	5533.17	1423.86	6325.64	1681.43	7567.46	2370.92
6	4199.88	1119.12	4906.97	1393.85	5516.75	1609.65
8	2754.78	971.69	3095.44	982.47	3448.62	1116.26
10	1910.95	802.63	2193.79	801.67	2405.49	894.82
12	1381.22	592.26	1586.43	683.70	1728.29	714.12
16	712.18	599.48	918.32	469.68	964.63	560.15
24	152.89	357.97	130.63	299.40	154.59	358.03
36	0.00	0.00	0.00	0.00	0.00	0.00

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 8. MEAN PLASMA FLURBIPROFEN LEVELS FOR TEST AND REFERENCE PRODUCTS (N=17)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.17	.	.	.
0.33	8.55	25.48	2.98
0.5	3.51	10.35	2.95
0.67	2.85	5.74	2.01
0.83	2.57	4.53	1.76
1	2.26	3.68	1.63
1.5	1.72	2.33	1.35
2	1.43	1.63	1.14
2.5	1.18	1.23	1.04
3	1.02	1.10	1.08
3.5	0.92	0.98	1.06
4	0.88	0.84	0.96
5	0.87	0.73	0.84
6	0.86	0.76	0.89
8	0.89	0.80	0.90
10	0.87	0.79	0.91
12	0.87	0.80	0.92
16	0.78	0.74	0.95
24	1.17	0.99	0.84
36	.	.	.

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 9. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, N=17)

UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	73122.47	18285.26	68208.35	15075.04	69395.12	15312.48
AUCT	68056.71	16030.57	63075.18	13686.56	63587.24	13357.74
CMAX	15345.82	1933.76	11973.38	2805.45	11709.29	2594.46
KE	0.18	0.05	0.17	0.05	0.17	0.05
LAUCI	71233.23	0.23	66848.06	0.20	67985.21	0.20
LAUCT	66485.34	0.22	61881.18	0.19	62436.44	0.19
LCMAX	15239.87	0.12	11690.09	0.22	11453.66	0.21
THALF	4.15	1.36	4.34	1.11	4.31	1.23
TMAX	1.47	0.64	2.55	1.10	3.02	1.13

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 10. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)

UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.07	1.05	0.98
AUCT	1.08	1.07	0.99
CMAX	1.28	1.31	1.02
KE	1.07	1.05	0.98
LAUCI	1.07	1.05	0.98
LAUCT	1.07	1.06	0.99
LCMAX	1.30	1.33	1.02
THALF	0.95	0.96	1.01
TMAX	0.58	0.49	0.84

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 11. LSMEANS AND 90% CONFIDENCE INTERVALS (N=17)

UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	72539.38	67619.55	68713.85	104.28	110.27	102.62
AUCT	67583.95	62568.90	63052.38	105.13	110.90	104.32
CMAX	15485.84	12078.36	11834.39	117.90	138.52	120.34
LAUCI	70628.35	66259.93	67316.23	103.79	109.47	102.16
LAUCT	65999.64	61385.81	61923.13	104.68	110.43	103.77
LCMAX	15392.40	11785.58	11565.04	118.64	143.77	120.91

1=TEST FASTING; 2=TEST FED; 3=REFERENCE FED

TABLE 12. LSMEANS AND 90% CONFIDENCE INTERVALS (N=17)

UNIT: AUC=NG.HR/ML CMAX=NG/ML TMAX=HR

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	108.52	95.46	101.36
AUCT	110.05	96.37	102.10
CMAX	141.37	91.54	112.58
LAUCI	107.76	95.84	101.09
LAUCT	109.47	96.52	101.82
LCMAX	146.51	92.58	112.18

III. *IN VITRO* RESULTS (DISSOLUTION):

See Table 13 below. The dissolution data are acceptable.

TABLE 13. *In Vitro* Dissolution Testing (Non-USP, FDA Method)

A. Conditions

Method, Apparatus II Paddle RPM: 50 No. of Units: 12
Medium: Phosphate Buffer, pH 7.2 Volume: 900 mL
Reference Drug: Ansaid^R Manufacturer: The Upjohn Co.
Assay Methodology: Not indicated

B. Results

Sampling Time (Minutes)	Test Product			Reference Product		
	Mean % Dissol	Range	CV	Mean % Dissol	Range	CV
	Lot # 93-022T			Lot # 198JC		
	Strength 100 MG					
5	86.9		6.9	—	—	—
10	97.4		1.4	87.4		2.2
20	97.6		1.4	93.9		2.1
30	97.4		1.6	95.6		1.7
45	97.4		1.5	96.4		2.1

IV. DEFICIENCIES: None

V. RECOMMENDATIONS

1. The single dose non-fasting study conducted by Sidmak Laboratories, Inc. on its flurbiprofen tablets, 100 mg, Lot # 93-022T comparing it with Upjohn's Ansaid^R 100 mg tablets, Lot #198JC, has been found acceptable.

2. The firm has previously conducted an acceptable single dose fasting study on its flurbiprofen tablets, 100 mg, Lot # 93-022T comparing it with Upjohn's Ansaid^R 100 mg tablets, Lot # 482YP (Re: Review, Shrivastava, 8/31/95).

The studies demonstrate that Sidmak Laboratories' flurbiprofen, 100 mg tablets, are bioequivalent to the reference product. Ansaid^R 100 mg tablets, manufactured by Upjohn.

3. Comparative dissolution testings conducted by Sidmak Laboratories, Inc. on its flurbiprofen 100 mg tablets, Lot # 93-022T, and Upjohn's Ansaid^R 100 mg Tablets, Lot #198JC, are

acceptable.

4. The firm has previously conducted acceptable dissolution testings on its flurbiprofen 100 mg and 50 mg tablets, Lot # 93-022T and 93-024T, respectively (Re: Review. Shrivastava. 8/31/95).

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL phosphate buffer, pH 7.2 using USP XXIII methods and Apparatus II (Paddle) at 50 r.p.m. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of flurbiprofen is dissolved in 45 minutes.

5. The formulation for the 50 mg tablet strength is proportionally similar to the 100 mg strength of the test product, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 50 mg tablets is granted. The 50 mg tablets of the test product is, therefore, deemed bioequivalent to the Ansaïd^R tablets, 50 mg, manufactured by Upjohn Co.

From the bioequivalence point of view, the firm has met the *in vivo* bioavailability, and *in vitro* dissolution testing requirements for its flurbiprofen 100 mg and 50 mg tablets, and the application is approvable.

The firm should be informed of the recommendations.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED S Nerurkar
FT INITIALED S Nerurkar

Date 11/26/1996

Concur: _____ Date: 11/26/96

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Attachments-7

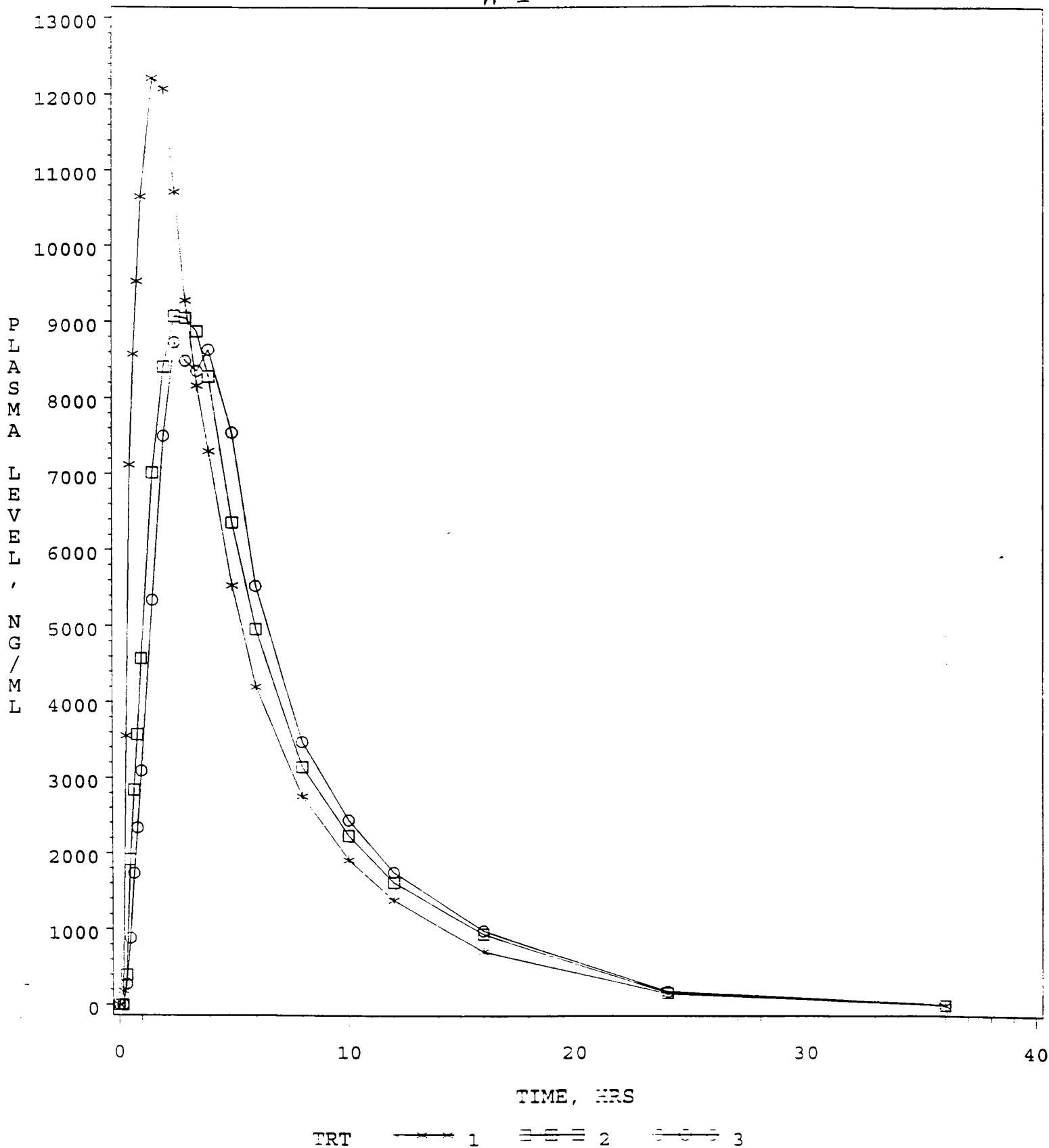
FIG P-2. PLASMA FLURBIPROFEN LEVELS

FLURBIPROFEN TABLETS, 100 MG, ANDA = 74-647

UNDER NON-FASTING CONDITIONS

DOSE=1 X 100 MG

n =



1=TEST FASTING (SIDMAK) 2=TEST FED (SIDMAK) 3=REFERENCE FED (UPJOHN)

31-01-1996

10:35

Table 1
Project No: 930162
Summary of Results - FLURBIPROFEN in Plasma
Pharmacokinetic Parameters
(N = 18)

	In AUC 0-t* (ng·h/mL)	In AUCinf* (ng·h/mL)	In Cmax* (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Sidmak (fasted) (A)						
Mean	66485.45	71233.45	15239.877	1.471	0.1828	4.146
CV	22.0	23.3	12.0	43.4	29.2	32.9
n	17	17	17	17	17	17
Sidmak (fed) (B)						
Mean	62488.67	67509.93	11551.357	2.547	0.1673	4.452
CV	19.5	20.1	22.4	42.0	30.2	26.5
n	18	18	18	18	18	18
Upjohn (fed) (C)						
Mean	63286.31	68818.16	11350.173	3.018	0.1713	4.396
CV	19.6	20.7	21.4	36.3	31.3	28.5
n	18	18	18	18	18	18
Least-Squares Means						
Sidmak (fasted) (A)	67659.25	72481.46	15362.333			
Sidmak (fed) (B)	62630.52	67492.10	11543.113			
Upjohn (fed) (C)	62839.58	68490.91	11178.806			
Ratio of Least Squares Means						
(B/A)%	92.6	93.1	75.1			
(B/C)%	99.7	98.5	103.3			

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
Subject No. 12 did not complete the crossover (Period 3, Form A).

DEFAULT

31-01-1996

10:34

Table 2
Project No: 930162
Summary of Results - FLURBIPROFEN in Plasma
Pharmacokinetic Parameters
(N = 18)

	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)
Sidnak (fasted) (A)			
Mean	68056.7	73122.6	15345.82
CV	23.6	25.0	12.6
n	17	17	17
Sidnak (fed) (B)			
Mean	63669.7	68853.4	11832.04
CV	21.2	21.6	23.6
n	18	18	18
Upjohn (fed) (C)			
Mean	64479.0	70242.4	11599.17
CV	20.9	21.8	22.1
n	18	18	18
Least-Squares Means			
Sidnak (fasted) (A)	69192.1	74335.0	15471.80
Sidnak (fed) (B)	63766.7	68769.0	11835.14
Upjohn (fed) (C)	64058.2	69954.7	11388.16
Ratio of			
Least-Squares Means			
(B/A)%	92.2	92.5	76.5
(B/C)%	99.5	98.3	103.9

Subject No. 12 did not complete the crossover (Period 3, Form A).

DEFAULT

Attachment 2

31-01-1996

10:30

Table D6
Project Number :930162
FLURBIPROFEN in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Upjohn (fed) (C)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1	1	63690	71247	89.4	11990.8	2.00	0.150	4.61	5.00	16.00
2	1	59599	67299	88.6	12447.9	5.00	0.164	4.23	8.00	16.00
3	3	56046	62558	89.6	14851.1	4.00	0.176	3.95	6.00	16.00
4	2	48497	50504	96.0	12239.9	2.00	0.307	2.26	4.00	12.00
5	2	67599	73121	92.4	15681.9	2.50	0.154	4.50	6.00	16.23
6	2	46260	48697	95.0	7788.0	2.50	0.209	3.31	6.00	16.00
7	2	55038	57345	96.0	12940.6	2.00	0.220	3.15	5.00	16.00
8	1	57566	63056	91.3	9671.1	5.00	0.184	3.77	6.00	16.00
9	1	93944	103438	90.8	11941.4	4.00	0.107	6.48	8.05	24.00
10	3	62336	67353	92.6	10564.2	3.00	0.178	3.90	6.00	16.00
11	1	54990	58681	93.7	8896.1	2.50	0.186	3.73	6.00	16.00
12	2	79640	86647	94.1	9727.2	3.00	0.118	5.89	8.00	24.00
13	3	71128	75885	93.7	9214.7	3.50	0.117	5.94	8.00	24.00
14	2	59698	64586	92.4	17762.5	2.50	0.266	2.61	3.50	12.00
15	3	61439	66919	91.8	12315.4	0.83	0.160	4.34	5.00	16.00
16	1	61659	69075	89.3	9501.2	3.50	0.154	4.49	5.00	16.00
17	3	95953	106037	90.5	11048.8	4.00	0.105	6.61	8.00	24.00
18	3	65541	73916	88.7	10202.3	2.50	0.129	5.37	8.00	16.00
Arithmetic Mean		64479.0	70242.4	91.99	11599.17	3.018	0.1713	4.396		
± SD		13500.02	15284.01	2.415	2559.986	1.0969	0.05358	1.2521		
CV%		20.9	21.8	2.6	22.1	36.3	31.3	28.5		
n		18	18	18	18	18	18	18		

DEFAULT

Attachment -

Flurbiprofen Tablets, USP
50 mg & 100 mg
ANDA # 74-647
Reviewer: S.P. Shrivastava
WP # 74647SDW.395

AUG 31 1995

Sidmak Laboratories, Inc.
East Hanover, NJ
Submission Date:
March 14, 1995

**Review of Bioequivalence Studies, Dissolution Data
and Waiver Request**

I. Background:

Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis and osteoarthritis. Flurbiprofen inhibits prostaglandin synthesis, which may be associated with its mechanism of action. Virtually all of the anti-inflammatory activity of flurbiprofen is present in the S-(+)-enantiomer. The available evidence from human studies indicates that R-flurbiprofen does not undergo the *in vivo* irreversible inversion to the S-enantiomer that has been observed in other NSAID's of the 2-arylpropionic acid class.

Flurbiprofen is rapidly absorbed following oral administration with T_{max} ranging 0.5 to 4 hrs. Food may decrease C_{max} (27-32%) by delaying absorption but does not significantly change the extent of absorption as measured by AUC. In one study, flurbiprofen absorption was found to be bimodal after administration of the tablet form in the fasted (on water) or fed (on apple juice) state. In this study, the lag time before the onset of the second absorption phase was dependent on the gastric emptying time.

Flurbiprofen is greater than 99% bound to plasma proteins (albumin). The binding has been reported to be minimally nonlinear over the concentration ranges encountered clinically. In one study, however, AUC_{0-Inf} was found increased linearly over the dose range of 100-300 mg. Flurbiprofen elimination from plasma appears biphasic, with terminal half-life values reported from 3 to 7 hours. The major route of elimination is hepatic clearance, with 95% of a daily dose excreted in urine in 24 hours, either as unchanged drug (20-25%), or as three metabolites: 4'-hydroxy (40-47%), 3'-hydroxy-4'-methoxy (20-30%), and 3',4'-dihydroxy (5%). The 4'-hydroxy metabolite showed low pharmacological activity in animal models.

Common adverse reactions from flurbiprofen include dyspepsia, diarrhea, abdominal pain, nausea, headache, signs and symptoms suggesting urinary tract infection and edema.

Flurbiprofen is currently marketed as Ansaïd[®], 50 and 100 mg tablets, manufactured by Upjohn.

The firm has submitted the results of a single-dose, fasting bioequivalence study comparing Upjohn's Ansaïd[®] Tablets, 100 mg, with Sidmak Laboratories' flurbiprofen tablets, 100 mg. The firm has also submitted the comparative dissolution data for the above products as well as

3. Results

Pharmacokinetic Parameters

- Pharmacokinetic parameters are given in Tables 1-4.
- ANOVA analysis did not show any significant treatment or sequence effect on AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , or T_{max} .
- The test/reference ratios for all PK parameters (average) for the products were within 0.88-1.03 (Table 1).
- The 90% CIs for $LAUC_{0-t}$, $LAUC_{0-\infty}$ and LC_{max} were within 80-125% (Table 1).
- Data for all 24 subjects were used in the computation of PK parameters.
- Ratios of individual $AUC_{0-t}/AUC_{0-\infty}$ averaged 0.95 (range: 0.92-0.96) for Sidmak, and 0.95 (0.91-0.96) for Upjohn product, respectively (Tables 2, 3).
- Spot check of firm's calculations indicated that AUCs, $T_{1/2}$ and K_{el} calculations were appropriate.

- The average of individual T/R ratios for AUC_{0-t} , AUC_{inf} and C_{max} were 1.02 (range: 0.84-1.17), 1.01 (range: 0.84-1.14), and 1.05 (range 0.73-2.26), respectively (Tables 4, 5, 6).
- The T/R ratio for mean plasma concentration during 0-36 hours sampling times varied between 0.88-1.25 and the overall average was 1.04 (Table 7).

Table 1. Mean (%CV) Pharmacokinetic Parameters (n = 24)

Parameter	Test-A	Ref-B	Ratio, T_A/R_B	90% CI
AUC_{0-T} , $\mu\text{g}\cdot\text{Hr}/\text{mL}$	70.69 (21.2)	69.63 (19.8)	1.015	98.6-104.5
AUC_{0-inf} , $\mu\text{g}\cdot\text{Hr}/\text{mL}$	74.67 (21.4)	73.49 (19.7)	1.016	98.6-104.6
C_{max} , $\mu\text{g}/\text{mL}$	16.12 (15.7)	15.89 (20.0)	1.015	95.1-107.8
$LAUC_{0-t}$, $\mu\text{g}\cdot\text{Hr}/\text{mL}$	4.238	4.225	1.013	98.5-104.2
$LAUC_{0-inf}$, $\mu\text{g}\cdot\text{Hr}/\text{mL}$	4.292	4.279	1.013	98.5-104.2
LC_{max} , $\mu\text{g}/\text{mL}$	2.769	2.744	1.025	95.2-110.2
T_{max} , Hr	1.375 (52.5)	1.570 (82.9)	0.876	
$T_{1/2}$, Hr	3.67 (21.7)	3.59 (17.8)	1.02	
K_{el} , Hr^{-1}	0.1964 (18.6)	0.1986 (16.1)	0.99	

03-12-1993

Table D3

Project Number : 901640

Flurbiprofen In Plasma

Pharmacokinetic Parameters by Formulation

Formulation: Sidmak (A)

16:34

Subject ID	Period	AUC 0-t (mcg-h/mL)	AUC Inf (mcg-h/mL)	AUC/AUC Inf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	kel Start (h)	kel Stop (h)	Half-life (h)
1	2									
2	1									
3	1									
4	2									
5	1									
6	2									
7	1									
8	1									
9	2									
10	1									
11	2									
12	2									
13	1									
14	1									
15	2									
16	1									
17	2									
18	2									
19	1									
20	2									
21	1									
22	1									
23	2									
24	2									
Arithmetic Mean										
		70.69	74.67	94.71	16.1234	1.375	0.1964			3.666
± SD		14.955	15.987	1.120	2.52455	0.7224	0.03650			0.7946
CV%		21.2	21.4	1.2	15.7	52.5	18.6			21.7
n		24	24	24	24	24	24			24

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03-12-1993

16:34

Table D4
Project Number :901640
Flurbiprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Upjohn (B)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	kel (1/h)	kel Start (h)	kel Stop (h)	Half-life (h)
1	1									
2	2									
3	2									
4	1									
5	2									
6	1									
7	2									
8	2									
9	1									
10	2									
11	1									
12	1									
13	2									
14	2									
15	1									
16	2									
17	1									
18	1									
19	2									
20	1									
21	2									
22	2									
23	1									
24	1									
Arithmetic Mean		69.63	73.49	94.73	15.8892	1.570	0.1986			3.585
± SD		13.791	14.478	1.374	3.17275	1.3024	0.03191			0.6394
CV%		19.8	19.7	1.5	20.0	82.9	16.1			17.8
n		24	24	24	24	24	24			24

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TABLE - 4

16:37

Table D5
 Project Number : 901640
 Flurbiprofen in Plasma
 Ratio Analysis - AUC 0-t (mcg-h/ml.)
 Sidmak (A) vs. Upjohn (B)

03-12-1993

(A/B)X

(B)

(A)

Subject

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

Arithmetic Mean 70.69
 s SD 14.955
 CV% 21.2
 n 24

69.63
 13.791
 19.8
 24

101.62
 7.975
 7.8
 24

DEFAULT

03-12-1993

Table D6

Project Number :901640

Flurbiprofen in Plasma

Ratio Analysis - AUCinf (mcg·h/mL)

Sidak (A) vs. Upjohn (B)

16:37

(A/B)X

(B)

(A)

Subject

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

Arithmetic Mean

74.67

± SD

15.987

CV%

21.6

n

24

73.49

14.478

19.7

24

101.63

7.086

7.0

24

DEFAULT

03-12-1993

16:37

Table D7
Project Number :901640
Flurbiprofen in Plasma
Ratio Analysis - Cmax (mcg/mL)
Sidnek (A) vs. Upjohn (B)

Subject	(A)	(B)	(A/B)*
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Arithmetic Mean	16.1234	15.8892	105.01
± SD	2.52455	3.17275	28.324
CV%	15.7	20.0	27.0
n	24	24	24

DEFAULT

TABLE 7. Mean Plasma Concentration at Each Sampling Time Point
(n = 24)

TIME (HR)	TEST	CV (%)	REFERENCE	CV (%)	Ratio, T/R
Pre-dose	0.00		0.00		
0.33	6.98	82.3	5.62	90.8	1.25
0.67	11.35	52.3	10.70	63.1	1.06
1.00	12.60	42.5	11.24	54.8	1.12
1.50	12.80	25.8	10.88	44.8	1.18
2.00	11.85	26.4	11.26	34.5	1.05
2.50	10.28	27.7	10.37	34.8	0.99
3.00	8.93	26.1	8.91	29.0	1.00
3.50	8.17	24.0	7.85	26.1	1.04
4.00	7.33	25.0	7.18	26.6	1.02
6.00	3.96	27.1	4.51	44.2	0.88
8.00	2.78	31.2	2.91	37.4	0.96
12.00	1.38	37.0	1.45	44.4	0.95
16.00	0.74	64.3	0.75	58.5	0.99
24.00	0.08	277.4	0.08	278.7	1.00
36.00	0.00	----	0.00	----	----

4. Adverse Effects: See Table below:

Sign/Symptom	Test	Reference	Drug Related
Backache	1	0	No
Sore Throat	1	0	No
Headache	1	0	No
Stomach Burn	1	0	Possible
Cough	0	1	No
Nasal Congestion	0	1	No
Diaphoretic	0	1	No
Dizziness	0	1	No

The medical officer did not find any adverse reaction to be serious, and none were given any medication to recover.

5. Formulation: See the Table 8 below.

**TABLE 8. Comparison of Reference and Test Product Formulations
(Amounts in mg/Tablet)**

Ingredients	Test 50 MG	Test 100 MG	Reference 100 MG
Flurbiprofen, USP	50	100.0	100
Lactose anhydrous, NF, DT			
Crospovidone, NF			
Pregelatinized Starch, NF			
Purified Water, USP			
Microcrystalline cellulose, NF			
Croscarmellose Sodium, NF			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
Silicon Dioxide			
Croscarmellose Sodium			
Carnauba Wax			
Hydroxypropyl Methylcellulose			
Propylene Glycol			
Titanium Dioxide			
Dye FDC Blue #2			

Coating and Printing:

	White	Green
Clear**		
Carnauba Wax Powder, NF		
Purified Water, USP		
Black Ink***		
Purified Water, USP (q.s.)		
Isopropyl Alcohol, USP (q.s.)		

Theoretical Weight	238.925 mg	477.85 mg
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III. *In Vitro* Results (Dissolution): See Table 9 below.

Gen. Drug Name: Flurbiprofen

Firm: Sidmak, Inc.

ANDA # 74-647

Submission Date: March 14, 1995

TABLE 9. *In Vitro* Dissolution Testing

A. **Conditions**

Method, Apparatus II Paddle RPM: 50 No. of Units: 12
Medium: Phosphate Buffer, pH 7.2 Volume: 900 mL
Reference Drug: Ansaïd^R Manufacturer: The Upjohn Co.
Assay Methodology: Not indicated

B. **Results**

<u>Sampling Time</u>	<u>Test Product</u>			<u>Reference Product</u>		
(Minutes)	<u>Mean % Dissol</u>	<u>Range</u>	<u>CV</u>	<u>Mean % Dissol</u>	<u>Range</u>	<u>CV</u>
	Lot 93-024T			Lot # 003YY		
		<u>Strength 50 MG</u>				
5	92.5		5.4	78.8		8.9
10	98.1		1.5	90.7		6.3
20	98.7		1.5	94.4		4.0
30	98.6		1.4	95.6		3.7
45	98.7		1.5	96.5		3.7

	Lot # 93-022T	<u>Strength 100 MG</u>	Lot # 482YP	
5	86.9	6.9	82.1	5.7
10	97.4	1.4	96.9	1.3
20	97.6	1.4	98.9	1.4
30	97.4	1.6	98.4	1.5
45	97.4	1.5	99.0	1.2

IV. Comments:

1. The firm has not submitted data for the limited food study comparing Sidmak flurbiprofen, 100 mg tablets with Upjohn's Ansaid^R 100 mg tablets. The food study is required to establish the bioequivalence of flurbiprofen tablets.

2. For the final study report, the sponsor should submit a diskette in ASCII format containing two separate files configured as follows:

A: SUBJ SEQ PER TRT AUC_{0-T} AUC_{INF} C_{max} T_{max} K_{el} T_{half}

B: SUBJ SEQ PER TRT C1, C2, C3.....Cn (concentrations at sampling times)

V. Recommendations:

1. The single dose fasting study conducted by Sidmak Laboratories, Inc. on its flurbiprofen tablets, 100 mg, Lot # 93-022T comparing it with Upjohn's Ansaid^R 100 mg Tablets, Lot # 482YP has been found acceptable.

2. The dissolution testings conducted by Sidmak Laboratories, Inc. on its flurbiprofen 100 mg and 50 mg tablets, (Lot # 93-022T and 93-024T), are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL phosphate buffer, pH 7.2 using USP XXIII methods and Apparatus II (Paddle) at 50 r.p.m. The test product should meet the following specifications:

Not less than -- Q) of the labeled amount of flurbiprofen is dissolved in 45 minutes.

3. From the bioequivalence point of view, the firm has not met the *in vivo* bioavailability requirements for its flurbiprofen 100 mg and 50 mg tablets and the request for waiver for 50 mg tablets is denied due to deficiencies indicated in comment 1.

The firm should be informed of the above comments and recommendations. A copy of the Bioequivalence Guidance for Flurbiprofen Tablets should also be enclosed.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

— Date 8/31/95

Concu: _____ Date: _____

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Attachments-5

SPS/sps/8-26-95/74647SDW.395

cc: ANDA #74647 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-344
(CViswanathan), HFD-655 (Patnaik, Shrivastava), Drug File, Division File